

REMARKS/ARGUMENTS

Claims 1-13 were originally filed. Claims 1-13 are now pending in this application

Applicant respectfully requests reconsideration of the pending rejections and reexamination of the present application in view of the following remarks.

Claim Objections

Claim 2, 9, 12 are objected to under 37 CFR 1.75 (c) as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant respectfully traverses.

Examiner indicated that Claim 2 does not indicate the amount of acceptable component. 37 CFR 1.75 (c) states that “claims may be in dependent form, referring back to and further limiting another claim in the same application.” Examiner is respectfully reminded while Claim 1 claims a *composition* wherein some ingredients of the composition are between certain % of the total weight of the composition, Claim 2 further limits Claim 1 by claiming the single *dosage* of the composition of claim 1 characterized by the actual weigh of some of the ingredients in Claim 1. Referring to page 5 of the specification, “Wt %” refers to % pf the ingredients as a proportion of the total weight of the composition while Claim 2 claims “a dose of the composition ofclaim 1.”

Examiner further indicated that claim 9 and 12 do not indicate that composition contains said component, copper selenium or manganese. Applicant submits that while Claim 8 and 11 claim method of treatment with an effective amount of composition in

Claim 1, Claim 9 and 12 further *defines* the effective amount of the composition in Claim 1 based on range of certain ingredients, namely lysine, proline, arginine, Vitamin C, magnesium, green tea extract and N-acetyl-cysteine.

Accordingly, even though Claim 9 and 12 do not define the effective amount copper, selenium, and manganese of Claim 1, Claim 9 and 12 do indicate that composition of Claim 1 contains copper selenium or manganese. Applicant therefore submits that Claim 2, 9 and 12 are proper dependent claims for they do further limit the subject matter of previous claims.

Accordingly, withdrawal of this objection is respectfully requested.

Claims rejection – 35 USC § 103 (“Boulos, Gavish and Tedeschi”)

Claims 1-13 are rejected under 35 USC § 103(a) as allegedly being obvious over Boulos et al. (US Pat. 6,904,073) in view of Tedeschi et al. (Acad.Sci. 2002 Vol. 973, pp. 435-437) and Gavish et al. (Lipoprotein (a) reduction by N-acetylcysteine, Lancet 1991, Vol 337, pp.204.) Applicant respectfully traverses these rejections and requests that they be withdrawn.

The rejection of composition claims 1-7

While Boulos et al. disclose composition containing lysine, proline, arginine, Vitamin C, magnesium, green tea, selenium, copper, manganese, various excipients, it fails to disclose the specific composition as in claim 1.

Gavish et al. disclose that high level of lipoprotein (a) is associated with atherosclerotic disease and that administration of N-acetyl-cystine was effective in lowering plasma levels of lipoprotein (a). Gavish fails to disclose the specific composition as in claim 1.

Tedeschi discloses that both Green Tea and vitamin C have anti-inflammatory activity. Tedeschi fails to disclose the specific composition as in claim 1.

To establish a *prima facie* obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to combine reference teachings. Second, there must be reasonable expectation of success. Third, the prior art references, when combined, must teach or suggest all the claimed limitations. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966)

There was no suggestion or motivation to combine reference teachings.

Here, the first basic criterion has not been met. Applicant submits that Boulos fails to teach or suggest the presently claimed composition. The Examiner does not point to any motivation or suggestion in Boulos et al to combine disclosed composition with N-acetyl cysteine. Likewise, no motivation or suggestion of such was found in Tedeschi et al. or Garvish et al. to combine them with Boulos.

Absent some teaching or suggestion, explicitly or implicitly found in Boulos, Garvish and Tedeschi, one of skill in the art would not be motivated to combine with other references to make the claimed combination. The Federal Circuit has stated that “obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching suggestion or incentive supporting the combination. *In re Geiger*, 815 F.2d 686.

Coupled with this provision is the additional requirement that the suggestion or motivation exist before the date of invention. Thus, it is incorrect for the Examiner to formulate the suggestion or motivation based on current knowledge; the Examiner must remove all knowledge that he or she has accumulated since the date of invention.

Failure of the Examiner to provide the necessary suggestion or motivation will create a presumption that the combination of references selected by the Examiner to support the obviousness rejection was based on hindsight. The invention that was made, however, does not make itself obvious; that suggestion or teaching must come from the prior art.

Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044.

Without some suggestion to combine the references from the prior arts, the *prima facie* obviousness rejections must fail.

Unexpected results rebut the prima facie case of non obviousness

Assuming *arguendo* that prima facie case of obviousness has been established by the Examiner, one way for a patent applicant to rebut is to make a showing of “unexpected results” to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. *In re Soni*, 54 F.3d 746.

The Examiner must consider comparative data in the specification in determining whether the claimed invention provides unexpected results. *In re Margolis*, 785 F.2d 1029.

With respect to the claimed composition, since Tedeschi discloses compositions already disclosed in Boulos, the unexpected results must come from the joining of Boulos with Gavish. While Boulos et al. disclose composition containing Amino Acid (lysine, proline, arginine,) Vitamin C, magnesium, green tea, selenium, copper, manganese, various excipients, it fails to disclose N-acetyl-cystine.

Fig. 3 of the application as filed clearly indicates that there is a substantial improved result when joining N-acetyl-cystine with the composition as disclosed by

Boulos. Specifically, as shown in Fig. 3, the effect of the claimed composition (XR296)(at 100 mcg/ml) of the present invention is compared to the effect of some of its individual components in concentrations present in XR296, on TNF α stimulated secretion of IL-6 in smooth muscle cells. IL-6 are mediators of basic inflammatory response, and therefore, the lower the expression of IL-6, the more effective the composition is. Effective inhibition of the expression of IL-6 in smooth muscle cells is a remedy in treating atherosclerosis and retarding the effects of low level chronic inflammation and inflammatory responses.

According to Fig.3, the effect of N-acetyl-cystine alone on the IL-6 content in the media was 95.17% of control. Conversely, the effect of amino acid (Lysine, Proline, and Arginine) and Ascorbic Acid (vitamin C) and EGCG (green tea) on the IL-6 content in the media was 75.72% of control. Thus, one of the ordinary skill in the art would have expected the combination of N-acetyl-cystine to Lysine, Proline, Arginine, Vitamin C and EGCG to have an effect on the IL-6 content in the media to be equivalent to 70.87% of control. Accordingly, the claimed composition created a synergistic effect on the IL-6 content in the media where only 58.19% of IL-6 to the control was shown.

Furthermore, the effect of amino acid (Lysine, Proline, and Arginine) and EGCG (green tea) on the IL-6 content in the media was 89.86% of control. One of the ordinary skill in the art would have expected the combination of N-acetyl-cystine to Lysine, Proline, Arginine and EGCG to have an effect on the IL-6 content in the media to be equivalent to 85.03% of control. Surprisingly, as indicated by Fig.3, the combination created has an effect on the IL-6 content to be only 74.60% to the control.

The fact that an invention provides results which would not have been expected by those skilled in the art is strong evidence in rebuttal of an assertion that the invention would have been obvious. *In re Klosak*, 455 F.2d 1077. Based on the disclosure in the specification, the unexpected result is sufficient in rebuttal the assertion that the invention is obvious.

For the foregoing reasons, Applicant respectfully submits that the rejection of Claims 1-7 should be withdrawn.

The rejection of method claims 8-10

Claims 8-10 are directed to methods for retardation of an inflammatory response in mammals, comprising the step of administering to a mammal in need of treatment an effective amount of the pharmaceutical composition of claim 1.

While Boulos et al. disclose a method of optimizing cardiovascular health with composition containing lysine, proline, arginine, Vitamin C, magnesium, green tea, selenium, copper, manganese, and various excipients; it fails to disclose a method to retard inflammatory response in mammals. It also fails to disclose a method in which the specific composition as disclosed in claim 1 is used.

Gavish et al. disclose that high level of lipoprotein (a) is associated with atherosclerotic disease and that administration of N-acetyl-cystine was effective in lowering plasma levels of lipoprotein (a). Gavish fails to disclose a method to treat inflammation.

Tedeschi discloses that both Green Tea and vitamin C have anti-inflammatory activity. Tecdeschi fails to disclose the method using specific composition as in claim 1.

To establish a *prima facie* obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to combine reference teachings. Second, there must be reasonable expectation of success. Third, the prior art references, when combined, must teach or suggest all the claimed limitations. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966)

There was no suggestion or motivation to combine reference teachings.

Here, the first basic criterion has not been met. Applicant submits that Boulos fails to teach or suggest the presently claimed method as it is directed to a method of optimizing cardiovascular health. The Examiner does not point to any motivation or suggestion in Boulos et al to combine the disclosed method with Tedeschi or Garvish. Likewise, no motivation or suggestion of such was found in Tedeschi et al. or Garvish et al. to combine them with Boulos.

Absent some teaching or suggestion, explicitly or implicitly found in Boulos, Garvish and Tedeschi, one of skill in the art would not be motivated to combine with other references to make the claimed combination.

Without some suggestion to combine the references from the prior arts, the *prima facie* obviousness rejections must fail.

There was no reasonable expectation of success.

The second basic criterion has not been met. Applicant submits that the Examiner failed to indicate how Boulos, Garvish and Tedeschi were able to provide a reasonable expectation of success with respect to modifying their disclosure to become our claimed method, mainly a method for retardation of an inflammatory response in mammals, comprising the step of administering to a mammal in need of treatment an effective amount of the pharmaceutical composition useful in alleviating pathological conditions in mammals, comprising lysine, proline, arginine, vitamin C, magnesium, green tea

extract, N-acetyl-cysteine, selenium, copper, manganese and one pharmaceutical acceptable component selected from the group consisting of a carrier, a diluent, and an excipient, wherein the pharmaceutical composition without the acceptable component contains 7-9 wt % magnesium, 20-30 wt % ascorbic acid and 11-25 wt % green tea extract.

Although it has been recently accepted that vascular and smooth muscle pathology manifested cardiovascular diseases is one of the inflammatory responses during atherosclerosis and hypertension, the opposite is not necessarily true. That is, a method of treating cardiovascular disease will not necessarily be successful in treating inflammation. Indeed, nothing in Boulous, Garvish would indicate that combining methods of treating retardation of atherosclerosis with method of treating inflammation would be collectively successful in retreating inflammation.

Without indicating some reasonable expectation of success, the *prima facie* obviousness rejections must fail.

Unexpected results rebut the prima facie case of non obviousness

With respect to the method of treating inflammation, Tedeschi discloses the anti-inflammatory action of Vitamin C and EGCG. Fig. 3 of the application as filed clearly indicates that there is a substantial improved result when joining Vitamin C and EGCG with the (Amino Acid) Lysine, Proline and Arginine. .

According to Fig.3, the effect of Vitamin C and EGCG alone on the IL-6 content in the media was 91.1% of control. Conversely, the effect of amino acid (Lysine, Proline, and Arginine) on the IL-6 content in the media was 95.47% of control. Thus, one of the ordinary skill in the art would have expected the combination of Lysine, Proline, Arginine, Vitamin C and EGCG to have an effect on the IL-6 content in the media to be equivalent to 86.57% of control. Accordingly, the claimed composition created a synergistic effect on the IL-6 content in the media where only 75.72% of IL-6 to the control was shown.

Further, the effect of N-acetyl-cystine alone on the IL-6 content in the media was 95.17% of control. On the other hand, the effect of amino acid (Lysine, Proline, and Arginine) and Ascorbic Acid (vitamin C) and EGCG (green tea) on the IL-6 content in the media was 75.72% of control. One of the ordinary skill in the art would have expected the combination of N-acetyl-cystine to Lysine, Proline, Arginine, Vitamin C and EGCG to have an effect on the IL-6 content in the media to be equivalent to 70.87% of control. Surprisingly, the claimed composition created a synergistic effect on the IL-6 content in the media where only 58.19% of IL-6 to the control was shown.

Based on the disclosure in the specification, the unexpected result is sufficient in rebuttal the assertion that the invention is obvious. For the foregoing reasons, Applicant respectfully submits that the rejection of Claims 8-10 should be withdrawn.

The rejection of method claims 11-13

Claims 11-13 are directed to methods for retardation of arteriosclerosis and atherosclerosis in mammals, comprising the step of administering to a mammal in need of treatment an effective amount of the pharmaceutical composition of claim 1.

While Boulos et al. disclose a method of optimizing cardiovascular health with composition containing lysine, proline, arginine, Vitamin C, magnesium, green tea, selenium, copper, manganese, and various excipients; it fails to disclose methods as disclosed in claims 11-13.

Gavish et al. disclose that high level of lipoprotein (a) is associated with atherosclerotic disease and that administration of N-acetyl-cystine was effective in

lowering plasma levels of lipoprotein (a). Gavish fails to disclose the method as disclosed in claims 11-13.

Tedeschi discloses that both Green Tea and vitamin C have anti-inflammatory activity. Tedeschi fails to disclose the methods as disclosed in claim 11-13.

There was no suggestion or motivation to combine reference teachings.

The Examiner does not point to any motivation or suggestion in Boulos et al to combine the disclosed method with Tedeschi or Garvish. Nothing in Boulos suggests to combined its disclosed any suggestion of combining composition it disclosed with N-acetyl-cystine for methods for retardation of arteriosclerosis and atherosclerosis in mammals. Likewise, no motivation or suggestion of such was found in Tedeschi et al. or Garvish et al. to combine them with Boulos.

Absent some teaching or suggestion, explicitly or implicitly found in Boulos, Garvish and Tedeschi, one of skill in the art would not be motivated to combine with other references to make the claimed combination.

Because no suggestions to combine the references from the prior arts are found, the *prima facie* obviousness rejections must fail.

Unexpected results rebut the prima facie case of non obviousness

With respect to the method of retardation of arteriosclerosis and atherosclerosis, Boulos et al. disclose method of optimizing cardiovascular health with composition containing lysine, proline, arginine, Vitamin C, magnesium, green tea, selenium, copper, manganese, various excipients, it fails to include N-acetyl-cystine as claimed by claims 11-13.

Gavish et al. disclose that high level of lipoprotein (a) is associated with atherosclerotic disease and that administration of N-acetyl-cystine was effective in lowering plasma levels of lipoprotein (a). Gavish fails to include lysine, proline, arginine, Vitamin C, magnesium, green tea, selenium, copper, manganese, and various excipients in its disclosure.

Fig. 3 of the application as filed clearly indicates that there is a substantial improved result in terms of inhibiting expression of IL-6 in smooth muscle cell where such inhibition will lead to treatment of atherosclerosis.

As shown in Fig. 3, the effect of the claimed composition (XR296)(at 100 mcg/ml) of the present invention is compared to the effect of some of its individual components in concentrations present in XR296, on TNF α stimulated secretion of IL-6 in smooth muscle cells. IL-6 are mediators of basic inflammatory response, and therefore, the lower the expression of IL-6, the better it is to remedy atherosclerosis.

According to Fig.3, the effect of N-acetyl-cystine alone on the IL-6 content in the media was 95.17% of control. Conversely, the effect of amino acid (Lysine, Proline, and Arginine) and Ascorbic Acid (vitamin C) and EGCG (green tea) on the IL-6 content in the media was 75.72% of control. Thus, one of the ordinary skill in the art would have expected the combination of N-acetyl-cystine to Lysine, Proline, Arginine, Vitamin C and EGCG to have an effect on the IL-6 content in the media to be equivalent to 70.87% of control. Accordingly, the claimed composition created a synergistic effect on the IL-6 content in the media where only 58.19% of IL-6 to the control was shown.

Further, the effect of amino acid (Lysine, Proline, and Arginine) and EGCG (green tea) on the IL-6 content in the media was 89.86% of control. One of the ordinary

skill in the art would have expected the combination of N-acetyl-cystine to Lysie, Proline, Arginine and EGCG to have an effect on the IL-6 content in the media to be equivalent to 85.03% of control. Surprisingly, as indicated by Fig.3, the combination created has an effect on the IL-6 content to be only 74.60% to the control.

Based on the disclosure in the specification, the unexpected result is sufficient in rebuttal the assertion that the invention is obvious.

For the foregoing reasons, Applicant respectfully submits that the rejection of Claims 11-13 should be withdrawn.

CONCLUSION

For at least the reasons set forth herein, Applicant respectfully submits that all the rejections have been overcome and all the pending claims are allowable. Accordingly, withdraw of the rejection and allowance of the present application is warranted. If the Examiner has any questions pertaining to this application or feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (650) 941-1196.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

By

Ali Kamarei, Esq.

Ali Kamarei, Esq.
280 Colorado Ave.
Palo Alto, CA 94301
Tel: (650) 941-1196

Reg. No. 37,000